Targeted next-generation sequencing demonstrates high frequency of MODY in Russian children

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Background: Maturity-onset diabetes of the young (MODY) is a heterogeneous group of disorders characterised by autosomal dominant type of inheritance and caused by genetic defects leading to dysfunction of pancreatic beta-cells. At least 13 types of MODY have been described in the literature, the most frequent of which are MODY types 1–3. The frequency of different MODY types in children in Russia has not been studied before.

Objective: To evaluate the contribution and molecular spectrum of mutations among MODY genes in Russian patients using a targeted NGS.

Methods: 796 patients with MODY phenotype (388 males, 408 females) were included in the study according to the inclusion criteria (diabetes or intermediate hyperglycemia; GAD, IAA, ICA, IA2 negative; preserved C-peptide secretion). 'Diabetes panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Interpretation of the sequencing results and assessment of the pathogenicity of sequence variants were performed according to the ACMG guidelines (2015).

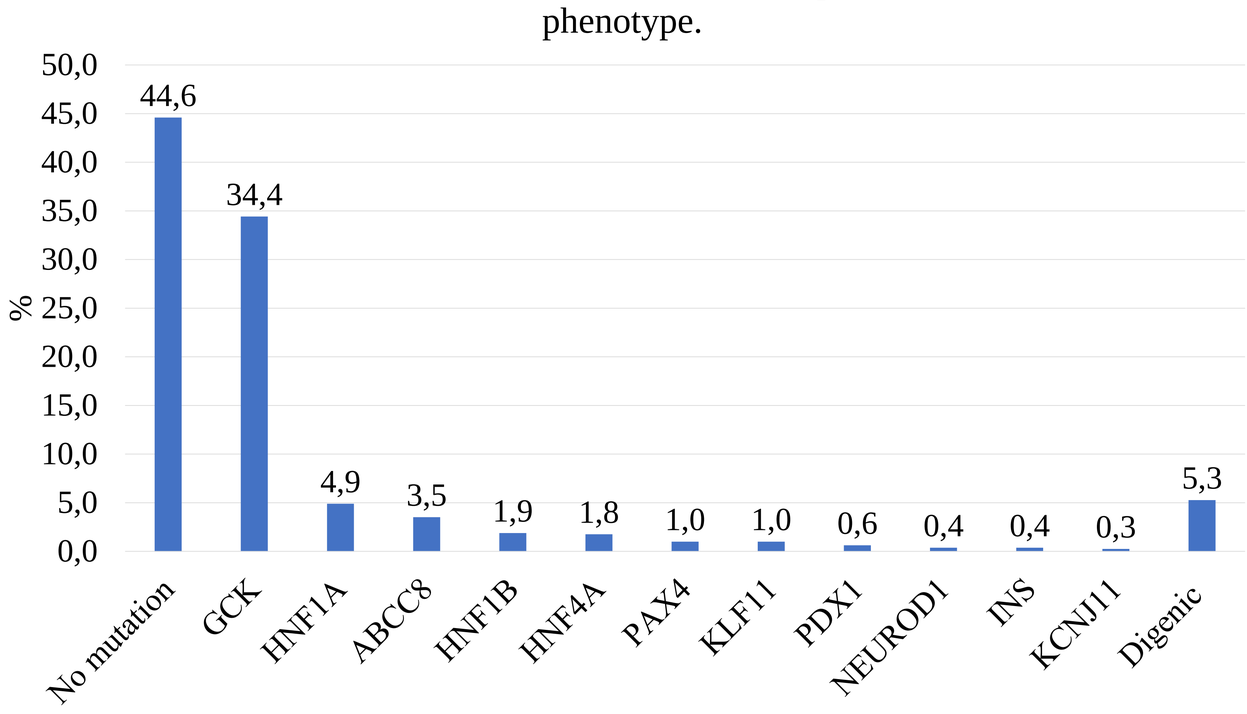
Results: 280 different sequence variants were identified in 441 patients (55.4%): 171 (61.1%) were classified as pathogenic, 55 (19.6%) - likely pathogenic and 54 (19.3%) variants of uncertain significance. The majority of variants were detected in *GCK* gene (34.4%, n=274/796).

Different sequence variants were detected in *HNF1A* (n=29/796, 4.9%), *ABCC8* (n=28/796, 3.5%), *HNF1B* (n=15/796, 1.9%), *HNF4A* (n=14/796, 1.8%), *KLF11* (n=8/796, 1.0%), *PAX4* (n=8/796, 1.0%), *PDX1* (n=5/796, 0.6%), *NEUROD2* (n=3/796, 0.4%), *INS* (n=3/796, 0.4%) *KCNJ11* (n=2/796, 0.3%). 7 patients had 2 mutations in in the same gene: *ABCC8* (n=4), *GCK* (n=2), *HNF1A* (n=1).

40 patients (5.0%) showed mutations in 2 genes. The most common combinations were *ABCC8+GCK* (n=5) and *INSR+GCK* (n=4). 2 patients (0.3%) had mutations in 3 genes: *HNF1B+INSR+PAX4; GCK+HNF1A+INSR*.

Conclusion. Targeted NGS in patients with MODY phenotype showed frequent sequence variants (55.4%) in genes associated with MODY. MODY2 was the most prevalent monogenic type of diabetes (34.4%) in our cohort. Some cases with different degrees of glucose intolerance were associated with digenic/oligogenic defects.

Distribution of nucleotide variants identified in patients with MODY phenotype.



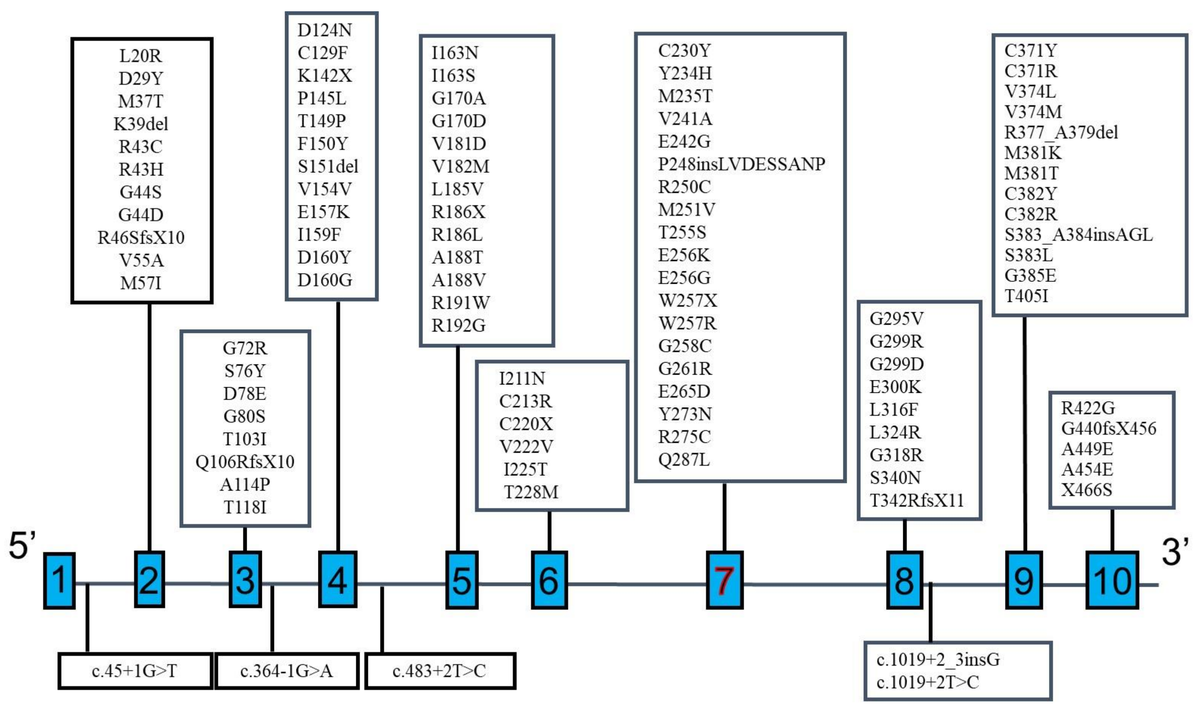


Fig.1. *GCK* mutations

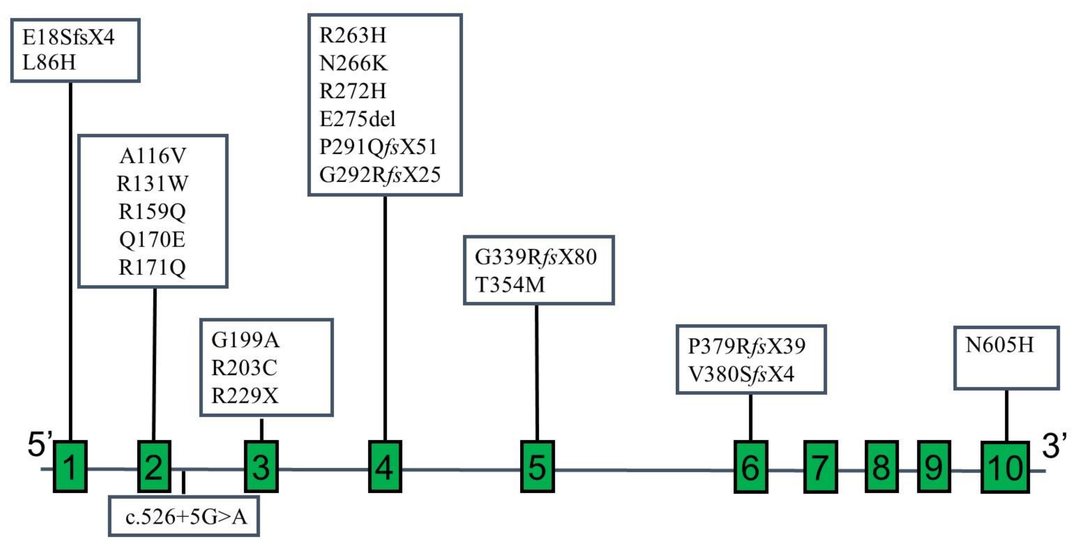


Fig.2. *HNF1A* mutations

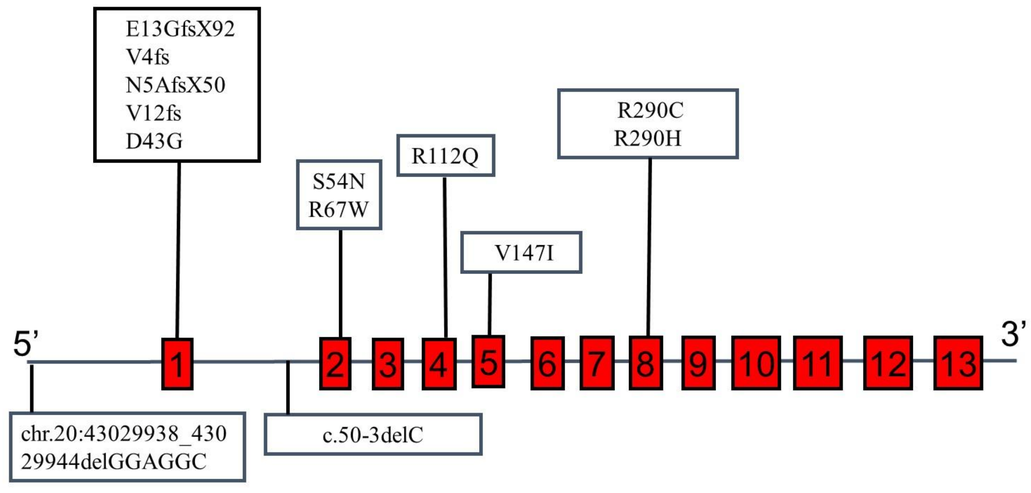


Fig.3. *HNF4A* mutations

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